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VESSEL ENLARGEMENT BY ARTERIOGENIC FACTOR DELIVERY

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VESSEL ENLARGEMENT BY ARTERIOGENIC FACTOR DELIVERY

BACKGROUND OF THE INVENTION

[0001] The present invention relates to induction of vessel enlargement. In particular, the present invention involves delivery of arteriogenic factors to cause structural enlargement of existing blood vessels.

BACKGROUND OF THE PRIOR ART

[0002] Coronary and peripheral arteries are naturally susceptible to atherosclerotic blockages (i.e. stenotic lesions). Both genetic and environmental factors play a role in the occurrence of atherosclerosis. The presence of an atherosclerotic blockage hampers circulation by occlusion of the affected vessel with plaque and smooth muscle cell build up. In the case of coronary arteries, such occlusions can lead to heart attacks and are potentially fatal. Impaired circulation in peripheral arteries is also accompanied with health risk.

[0003] Fortunately, the body is equipped with a natural defense mechanism, arteriogenesis, to help combat the effects of atherosclerosis. Arteriogenesis is the proliferative enlargement of pre-existing small collateral arteries, arterioles, or capillaries. For example, collateral arteries may branch off of an occluded larger artery near an occluded portion of the larger artery, thereby providing a natural bypass. This bypass is an alternative pathway for blood flow to that provided by the occluded larger artery. This alternative pathway (i.e. the collateral arteries) may naturally grow in response to the presence of the occlusion in the larger artery. Growth of such collateral arteries in this manner is generally known as arteriogenesis. Arteriogenesis may act in this manner to increase the size of the bypass and compensate for the decrease in circulation through the occluded artery.

[0004] Unfortunately, naturally occurring arteriogenesis is not always enough to compensate for the decrease in circulation through an occluded artery. In many cases, the rate and extent of occlusion build up is much greater than the body's ability to compensate with natural arteriogenesis. Where natural arteriogenesis is not enough to compensate for compromised circulation, medical intervention is required. Minimally invasive surgical procedures or more direct surgical bypass procedures (i.e. open heart surgery) may be required. These procedures may be coronary or peripheral, such as where treatment or bypass of the superficial femoral artery (SFA) is desired.

[0005] Minimally invasive procedures such as percutaneous transluminal coronary angioplasty (PTCA) are widely utilized. A PTCA procedure involves the insertion of an angioplasty balloon at the distal end of a catheter to the site of a stenotic lesion or occlusion in the larger artery. Once advanced, the balloon is inflated compressing the stenosis and widening the lumen in order to allow an efficient flow of blood through the lumen. Often, PTCA is followed by stent delivery to the site of the former stenosis. A stent is a tubular structure which provides support to the once narrowed artery to help maintain the now present widened state of the artery.

[0006] More direct bypass procedures, such as open heart surgery, are more traumatic for the patient but may be necessary where, for example, a PTCA procedure fails to have a more permanent vessel widening effect. The more traditional open heart surgical bypass requires the opening of the patient's chest cavity and the direct manipulation and grafting of vessel configurations to create a bypass around an occluded artery. Rehabilitation from such procedures is longer and more difficult for the patient.

[0007] Unfortunately, the success rate and availability of surgical intervention alone is limited. That is, in some cases neither invasive nor minimally invasive

procedures, as described above, are available to the patient as a treatment option. This is because minimally invasive treatment can fail to have a more permanent vessel widening effect as described above and due to the fact that many patients are not viable candidates for more invasive procedures. For example, a patient may be a diabetic with limited access for a minimally invasive surgical option, or unable to undergo the trauma associated with a more direct invasive bypass procedure as discussed above. Such a patient would not be a candidate for either the invasive or minimally invasive procedures discussed above. Therefore, what is desired is a method of delivering an arteriogenic factor to structurally enlarge an existing blood vessel.

SUMMARY OF THE INVENTION

[0008] An embodiment of the present invention provides a method of delivering an arteriogenic factor. The factor is delivered in a medically effective manner to structurally enlarge an existing blood vessel.

[0009] A method embodiment of structurally enlarging an existing blood vessel is provided where a distal portion of a catheter is advanced to an existing blood vessel. An arteriogenic factor is delivered to the existing blood vessel via said catheter in a medically effective manner.

[0010] In another embodiment of the invention an apparatus which includes an elongated catheter body having a distal portion is provided. The distal portion of the catheter is configured to deliver an arteriogenic factor to a vessel region in a medically effective manner to structurally enlarge an existing blood vessel.

BRIEF DESCRIPTION OF THE DRAWINGS

[0011] Fig. 1 is a cross sectional view of a vessel receiving extravascular treatment with an arteriogenic factor.

[0012] Fig. 2 is a cross sectional view of a vessel receiving intramural treatment with an arteriogenic factor.

[0013] Fig. 3 is a cross sectional view of a vessel receiving intravascular treatment with an arteriogenic factor.

[0014] Fig. 4 is a cross sectional view of a vessel having received treatment with an arteriogenic factor.

DETAILED DESCRIPTION OF THE INVENTION

[0015] While the background of the present invention is described with reference to certain methods of inducing arteriogenesis and devices, agents and other materials therefore, the invention is applicable to any medically effective induction of arteriogenesis. While the description makes reference to numerous specific details in order to provide a thorough understanding of the present invention, each specific detail need not be employed to practice the present invention. Additionally, well-known details, such as particular materials or methods, have not been described in order to avoid obscuring the present invention.

[0016] With reference to Figs. 1 and 2, embodiments of the present invention are shown. A primary vessel 2 is shown which is intended to deliver a flow of blood 4 to a target area 5, such as myocardium, by way of capillaries 10. However, the primary vessel 2 is impaired with an occlusion 3 such as a stenotic lesion. Such an occlusion 3 is often indicative of potentially widespread atherosclerosis. The occlusion 3 limits the flow of blood 4 through the primary vessel 2, thus, decreasing circulation and limiting the flow of blood 4 able to reach the target area 5.

[0017] In addition to the primary vessel 2, smaller bypass vessels 7, 8, 9 are present which provide a path for delivery of the flow of blood 4 to the target area 5. The bypass vessels 7, 8, 9 include a side branch 7, a tertiary branch 8, and a looping

branch 9. The bypass vessels 7, 8, 9 allow a manner of collateral circulation which can involve independent pathways to the target area 5. Alternatively, the bypass vessels 7, 8, 9 can provide a manner of bypassing the occlusion 3 and redelivering a flow of blood 4 to the primary vessel 2 as a means of providing access to the target area 5. Additionally, the bypass vessels 7, 8, 9 may have been angiogenically induced and not originally present prior to angiogenesis. Irrespective of prior angiogenic induction it is desirable to ensure the ability of a bypass vessel 7, 8, 9 to direct a flow of blood 4 to the target area 5. Thus, arteriogenesis is still desired.

[0018] The side branch 7 emanates from the primary vessel 2 at a particular position. This position is such that the flow of blood 4 has access to the side branch 7 prior to encountering the occlusion 3. The side branch 7 provides access to the target area 5 generally. Therefore, the flow of blood 4 which passes through the side branch 7 bypasses the occlusion 3 in order to reach the target area 5.

[0019] The tertiary branch 8 emanates from the side branch 7. The tertiary branch 8 provides access to the target area 5 generally and, in an alternate vessel configuration, can connect to the primary vessel 2 at a post occlusion position (not shown). The post occlusion position is such that where the flow of blood 4 travels through the tertiary branch 8, it bypasses the occlusion 3 in order to regain access to the primary vessel 2. Thus, the target area 5 is still provided with circulation via the primary vessel 2.

[0020] A looping branch 9 is shown emanating from the primary vessel 2 and terminating at the primary vessel 2. The looping branch 9 emanates and terminates with respect to the primary vessel 2 in a manner which provides a complete alternate route for a portion of the flow of blood 4 to bypass the occlusion 3. This bypass is similar to the tertiary branch 8 bypass in situations where the tertiary branch 8 connects

to the primary vessel 2 at a post occlusion position. That is, the flow of blood 4 is provided access back to the primary vessel 2 in order to reach the target area 5.

[0021] Although the bypass vessels 7, 8, 9 provide an alternate means of access to the target area 5, they are initially relatively small vessels in comparison to the primary vessel 2. Therefore, the bypass vessels 7, 8, 9 are not initially able to completely compensate for the lack of circulation provided to the target area 5 as a result of the occlusion 3. Therefore, in embodiments of the invention, treatment with an arteriogenic factor is introduced to increase the size of the bypass vessels 7, 8, 9. Increasing the size of the bypass vessels 7, 8, 9 allows for a more complete compensation for the lack of circulation provided through the primary vessel 2 as a result of the occlusion 3. For purposes of illustration, the vessel configuration of Figs. 1-4 are shown. However, in embodiments of the invention the following methods of encouraging arteriogenesis can be applied to any situation or vessel configuration where a target area 5 is receiving a less than desired blood supply and there is a desire to structurally enlarge a vessel which, prior thereto, supplies the target area 5 with the less than desired blood supply.

[0022] In embodiments of the invention, delivery of an arteriogenic factor to a vessel region is used to encourage arteriogenesis thereat. The induction of arteriogenesis includes an actual structural enlargement of the vessel involved (i.e. as opposed to a more temporary dilation). The arteriogenesis is induced in a medically effective manner in terms of delivery, dosage, and formulation of the arteriogenic factor.

[0023] By way of example, embodiments of inducing arteriogenesis are described here with reference to the side branch 7. However, in alternative embodiments arteriogenesis is induced as described herein to any vessel shown,

including the tertiary branch 8, the looping branch 9, or the primary vessel 2 itself. Additionally, in other alternative embodiments, treatment is enhanced by combining the types of arteriogenic factors which are delivered.

[0024] As shown in Figs. 1 and 2, a needle catheter 13 is advanced to the side branch 7. The needle catheter 13 delivers arteriogenic factor to act upon and induce arteriogenesis of the side branch 7.

[0025] The arteriogenic factor delivered in the embodiments of Figs. 1 and 2 is an arteriogenic chemical factor 11, such as a chemical, drug, protein, or gene construct. A gene construct will include a gene vector or naked DNA which encodes for a desired protein or agent that enhances an arteriogenic response by the side branch 7.

[0026] Arteriogenic chemical factors 11 delivered in embodiments of the invention include inflammatories. That is, inflammatories, which can enhance any of a cascade of inflammatory events, are often likely to lead to arteriogenesis due to a vessel's natural inflammatory response mechanism. Inflammatories which act as arteriogenic chemical factors 11 include naturally occurring classic mediators, blood-borne molecules, and cell-bound molecules.

[0027] Classic mediators include histamine and bradykinin. Blood-borne molecules that promote the recruitment of inflammatory cells include Complement Factor 5A, Platelet Activating Factor (PAF), prostaglandins, leukotrienes (such as leukotriene B4 (LTB4)), cytokines, (such as Interleukin 1 (IL-1) and Tumor Necrosis Factor (TNF)), and Monocyte Chemoattractant Protein (MCP-1). Cell-bound molecules include Intracellular Adhesion Molecules (ICAM's), Vascular Cell Adhesion Molecules (VCAM's), E selectin, P selectin, L selectin, and leukocyte integrins.

[0028] Alternative inflammatory compounds which induce arteriogenesis include endotoxins such as bacterial endotoxins. Bacterial endotoxins are lipo-

polysaccharides which promote inflammation. Heavy metal compounds such as iron or copper salts are used to induce an inflammatory response in alternative embodiments.

[0029] In another embodiment of the invention, an arteriogenic chemical factor 11 is introduced, such as NG-nitro L-arginine methyl ester (L-NAME) or asymmetric di-methyl arginine (ADME), which are not inflammatories. However, these particular factors increase the adhesive abilities of inflammatory cells. Additionally, Basic Fibroblast Growth Factor (B-FGF), which is also not an inflammatory, is used in an embodiment of the invention.

[0030] Delivery of an arteriogenic chemical factor 11 as described in the above embodiments can be in an amount of between about 0.01 nanogram and about 1 milligram per gram of tissue to be treated, with possible exception of the blood-borne molecules delivered intravascularly as discussed later herein. Additionally, embodiments of the invention include treatment with an immediate induction, while alternative embodiments include treatment over a predetermined duration of time (e.g. between about one and about five weeks). Treatment over a predetermined duration of time can be accomplished through several separate deliveries, preferably between about 3 and about 10 days apart from one another. In an alternative embodiment the administration of the arteriogenic chemical factor 11 is continuous by way of a controlled release.

[0031] In order to obtain a controlled release, the arteriogenic chemical factor 11 is incorporated with a performance enhancing additive in an embodiment of the invention. For example, the arteriogenic chemical factor 11 is suspended within, or as a part of, a microparticle to ensure treatment over a desired duration of time. The microparticle is a microsphere or microcapsule which is degradable at a designed rate. One such example is a polylactic acid membrane microparticle which contains the

desired arteriogenic chemical factor 11. In another alternative embodiment, the arteriogenic chemical factor 11 is incorporated with a liposome to obtain a desired rate of degredation. Other alternative embodiments utilize stabilizers, agents such as buffers, anti-oxidants, and protease inhibitors, that increase the stability of the arteriogenic chemical factor which are combined with the arteriogenic chemical factor 11.

[0032] Continuing with reference to Figs. 1 and 2, the needle catheter 13 is a catheter equipped with needles 14. The needles 14 deliver the arteriogenic chemical factor 11 to the vessel area.

[0033] Referring to Fig. 1, the vessel area to which the arteriogenic chemical factor 11 is delivered is an extravascular vessel area 15. That is, in the embodiment shown, it is desirable to induce arteriogenesis at a location that the side branch 7 does not yet occupy as a means of encouraging vascular growth outward toward that location.

[0034] Extravascular delivery is desirable where the vessel to undergo arteriogenesis is not readily accessible. For example, in an alternative embodiment, delivery of the arteriogenic chemical factor 11, by accessing the sizable side branch 7, is also used to effect arteriogenesis at the much smaller, and more difficult to access, tertiary branch 8. Delivery of arteriogenic chemical factor 11 to the extravascular vessel area 15, adjacent the tertiary branch 8, makes this possible. In other alternative embodiments, other extravascular vessel areas 15, such as within the pericardium generally, near the site of the occlusion 3, are treated in this manner to encourage arteriogenesis of the side branches 7, 8, 9 or the primary branch 2.

[0035] In other embodiments alternative devices are used to deliver the arteriogenic chemical factor 11. Catheters with specially designed drug delivery tips,

syringes and other non-catheter devices are used to deliver the arteriogenic chemical factor 11 to the extravascular vessel area 15 in these alternative embodiments.

[0036] Referring to Fig. 2, another alternative embodiment of the present invention is shown. In this embodiment it is desirable to act within the vessel itself to more directly induce arteriogenesis upon the side branch 7. That is, to act upon the intramural vessel area 20. Again, a needle catheter 13 is used. However, in other embodiments catheters with specially designed drug delivery tips, syringes or other non-catheter devices are used to deliver the arteriogenic chemical factor 11 to the intramural vessel area 20. Where a needle catheter 13 is used, the needles 14 are extended only to within the intramural vessel area 20 to deliver the arteriogenic chemical factor 11.

[0037] Referring to Fig. 3, an alternative embodiment of the invention is shown. In this embodiment a manner of delivering the arteriogenic chemical factor 11 intravascularly is shown. A porous balloon catheter 23 is used to deliver the arteriogenic chemical factor 11. Pores 30 are present which allow the porous balloon catheter 23 to release the arteriogenic chemical factor 11. The pores 30 are micropores if desired. A delivery as shown induces arteriogenesis by directing the arteriogenic chemical factor 11 at the vessel surface 27 which defines the intravascular vessel area 25. In one embodiment the delivery occurs slightly upstream of the portion of the vessel surface 27 to be treated with the understanding that the arteriogenic chemical factor 11 will migrate in the direction of the flow of blood 4.

[0038] In addition to the porous balloon catheter 23, other delivery devices are used in alternative embodiments to deliver the arteriogenic chemical factor 11 intravascularly. For example, in one embodiment a double balloon catheter, having occluding balloons spaced apart longitudinally, is used to deliver the arteriogenic

chemical factor 11 between the occluding balloons. In another alternative embodiment, a stent loaded with an arteriogenic chemical factor 11 is implanted within the side branch. As with other vessel areas 15, 20, a catheter with a specially designed drug delivery tip, a syringe, or other non-catheter device is used to deliver the arteriogenic chemical factor 11 to the intravascular vessel area 25 in other embodiments. Additionally, in one embodiment the needle catheter 13 of Figs. 1 and 2 is used for intravascular delivery where the needles 14 are extended only to within the intravascular vessel area 25.

[0039] Intravascular delivery of the arteriogenic chemical factor 11 is in an amount of between about 10 picograms to about 1 microgram per milliliter of blood (i.e. in the intravascular vessel area 25). Preferably, the arteriogenic chemical factor is a blood-borne molecule and the delivery occurs via a controlled and continuous release as described previously. However, the release need not be constant.

[0040] In addition to the more specific deliveries described above, in an alternative embodiment delivery is general and need not focus on a particular vessel area 15, 20, 25. Rather, delivery is directed generally into tissue and vasculature in an area of the occlusion 3, for example, by way of a syringe. Such a general delivery provides arteriogenic chemical factor 11 to one or more the vessel areas 15, 20, 25 simultaneously while also affecting multiple vessels 2, 7, 8, 9 simultaneously.

[0041] Alternative methods of introducing an arteriogenic physical factor are used in alternative embodiments. For example, in alternative embodiments catheters equipped with cutters or puncturing features, such as the needles 14 of Figs. 1 and 2, are used to focus acute injury on any portion of the vessel area to induce an inflammatory response and thus, arteriogenesis. The injury is the result of minor shear or compressive stress applied to the vessel surface 27. In other embodiments these

alternative devices are used to more directly effect injury beyond the vessel surface 27 and into the intramural vessel area 20 or the extravascular vessel area 15. For example, in one embodiment the needle catheter 13 of Figs. 1 and 2 is used to injure the vessel surface 27 (defining the intravascular vessel area 25), the intramural vessel area 20, and the extravascular vessel area 15 simultaneously. This is because the needles 14 are advanced into the extravascular vessel area 15 from within the intravascular area 25, affecting all vessel areas 15, 20, 25.

[0042] In addition to the above referenced arteriogenic factors, alternative embodiments utilize other arteriogenic factors. For example, in one embodiment an arteriogenic thermal factor is introduced. An arteriogenic thermal factor is introduced, for example, by way of a cryocatheter, having a distal portion of between about 0° Celsius (C) and about 10°C, and more preferably between about 0°C and about 4°C. The cryocatheter is briefly introduced to cause local injury to the vessel area making contact or close association with the distal portion of the cryocatheter. Alternatively, in another embodiment a heated catheter having a distal portion of between about 40° C and about 99° C, is introduced. In either case, an arteriogenic thermal factor can be introduced to cause an inflammatory response and induce arteriogenesis.

[0043] Referring to Fig. 4, the side branch 7 is shown following application of an arteriogenic factor thereto. The side branch 7 has been widened where the arteriogenic factor has been introduced. This increases the flow of blood 4 through the side branch and helps to compensate for the occlusion 3 within the primary vessel 2. Treatment with an arteriogenic factor is continued throughout the remainder of the side branch 7 until the occlusion 3 is compensated for with an enlarged bypass provided through arteriogenesis. In alternative embodiments the remaining vessels 2, 8, 9 are enlarged through arteriogenesis as described herein.

[0044] Embodiments of the invention include manners of increasing the rate of arteriogenesis such that a natural bypass or vascular widening is enhanced. Additionally, embodiments of the invention can be employed in minimally invasive manners to avoid undue trauma to a patient that can be associated with more invasive procedures such as open-heart surgery.

[0045] Although exemplary embodiments of the invention describe particular methods of delivering arteriogenic agents to a vessel area, other methods of the invention including alternate methods of delivery can be utilized. Many changes, modifications, and substitutions may be made without departing from the scope of this invention.